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THE CLINICAL VALUE OF EXPECTORANTS.

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The medical literature does not contain, so far as I have been able to determine, any accurate bedside observation on the value of expectorants. There are many references of medicial men's impressions, but nowhere carefully recorded facts that will bear close scrutiny. When an investigation of this subject was first considered, after reviewing the literature, several methods were considered and tried for an accurate bedside study of the subject. It was impossible, however, to obtain satisfactory data, so this was abandoned and the work carried on with the laboratory animal; and it would appear that an accurate bedside study of the action of expectorants offers at present insurmountable difficulties. Patients with acute bronchial troubles are unsuited for study on account of the rapid and marked spontaneous changes that may occur. Those with chronic bronchitis, where the daily or even weekly variations are imperceptible, are most suited for a study of this character. In these patients, however, it is apparently impossible to determine accurately the amount and viscosity of the sputum. The admixture of saliva and the length of time the secretion has remained in the trachea or bronchi, with consequent loss of water, must all be considered.

The review of the literature is comparatively simple, as the total published information upon this subject, outside of that contained in the text-books on pharmacology, is confined to less than a half dozen monographs. The total evidence at hand, therefore, consists of purely theoretical consideration and three or four series of observations performed upon laboratory animals, to which we have added some additional laboratory experiments.

Expectorants may be defined as agents which facilitate the removal of secretion from the air passages. Several factors play a role in this process. The act of coughing, by increasing air currents, carries upward the secretion in the trachea and larger bronchial tubes, but has no effect upon the bronchioles. In these latter the chief factor is the ciliary movements of the bronchial mucosa. It has been determined by Gebhart, Henderson and Taylor, and others that the ciliary activity is capable of carrying mucus 1.5 to 2.5 cm. per minute. Increased viscosity of the mucus interferes materially with this movement, and Engelmann has shown that it may entirely inhibit the action of the cilia. The third factor is the presence in the alveoli and smaller bronchioles of a peristaltic-like movement; this probably under vague control (Einthoven, Sandimann). These movements somewhat resembling intestinal peristalsis, are probably important factors in removing the mucus from the alveoli and terminal bronchioles, neither of which are provided with cilia. To facilitate removal of mucus it would, therefore, be necessary to stimulate coughing, increase the ciliary movements, lessen the viscosity of the secretion, or stimulate bronchial peristalsis.

The cilia are not supplied with nerves, and it is therefore impossible to stimulate them through the nervous system. Virchow, in 1854, demonstrated that the direct application of weak alkalies increased the activity of the cilia, and Rossbach claimed that alkalies by the mouth had the same effect. Cushney states that alkalies are not secreted through the bronchial mucosa, and certainly in the ordinary doses the amount so secreted must be neglible. It is, therefore, highly improbable that any of the expectorants increase the ciliary movement.

There is no evidence that any of the expectorants increase the rhythmical muscular contraction in the bronchioles. It is possible that apomorphin in large doses may stimulate the vagus and thus increase peristalsis.

The final possibility is the action of expectorants in thinning the bronchial secretion. The trachea and bronchi are richly supplied with mucous glands capable of producing a profuse secretion. The viscosity of this secretion may be lessened either by increasing the amount of secretion or by introducing into the secretion something which would dissolve the mucus, as for instance an alkali.

The expectorant action of ammonium chloride and ammonium carbonate was thought to be due to their elimination through the bronchial mucosa, the alkali thinning the secretion. This theory, however, will not bear close scrutiny. Biedl, Winterberg, and others have shown that one-half to four-fifths of the ammonia administered disappears in the liver, never reaching the systemic circulation. In the ordinary therapeutic dose of 0.3 gm. no more than 0.15 gm., or 2.5 grains, would reach the general circulation, and at most only a small part of this would be excreted by the bronchial mucosa, an amount certainly too small to modify the viscosity of the mucus. In case, therefore, the ammonium salts mentioned thin the mucous secretion they must act through some different channel. It is now believed that their action is upon the bronchial gland centre, which, in its activity, apparently shows a parallelism with the salivary centre. It is thought that the centre may be stimulated either directly by substances in the blood or reflexly from the stomach and mouth. Biedl and Winterberg have shown that in order to stimulate this centre in dogs it requires 2 to 2.5 mg. of ammonium salts per 100 gm. of blood. They found that when injected intravenously into a 7 kilo dog 0.48 gm. of ammonium chloride was required, and if given by the mouth twice this amount, equivalent to about 9 gm. in a man.

Turning to a consideration of the experimental work performed with ammonium salts, Rossbach, in 1882, endeavored to determine the amount of tracheal secretion in cats by exposing the interior of the trachea by means of a longitudinal slit and then observing the secretion directly. The exposed mucosa was dried with filter paper and the time noted in which secretion occurred. Drugs were then given and the secreting time again observed. He used large doses of ammonium carbonate, 2 gm. intravenously, and reported a definite delay in the secretion time. He also failed to increase secretion by painting the mucosa with a 1 per cent. solution of ammonium carbonate.

Calvert, in 1896, repeated Rossbach's experiments with quite different results. He refers to only two experiments, both on cats. He reports that after the intravenous injection of 2 gm. of sodium carbonate there was a shortening of the secretory time of one minute. Considering the method employed, namely, the covering of a previously dried surface with a secretion, this difference in time is too slight to enable us to draw any conclusions. Henderson and Taylor call attention to the late appearance of the secretion in one of Calvert's cases, thirty-seven minutes, as after an intravenous injection the effect should be noted within ten or twenty minutes. The possibility of such a surface being moistened by secretion carried up from below by the cilia makes another probable source of error.

Henderson and Taylor, in 1910, studied the action of expectorants by the following method: Cats were anesthetized with chloroform or ether, or both. This was followed by urethane, which kept the animal asleep during the period of observation. One limb of a Y-tube was fastened into the trachea, another to a calcium U-tube and the other limb to the blast side of a Meyer respiratory pump, the exhaust end of which was attached to the other end of the calcium

U-tube. The animal was placed upon its belly on an incline to assist in the escape of mucus. By this method not only the mucus but the water also contained in the expired air was estimated. This latter factor apparently introduces an element of error, as they found it varied with the temperature of the animal, the amount of air forced into the lung, and the state of the animal's circulation. They reported that ammonium carbonate or ammonium chloride in large doses given intravenously equivalent to 12 gm. for a 70 kilo man, caused marked increased secretion of mucus. Two and a half times this dose, an equivalent of 30 gm. for a man, given by the mouth, also caused increased secretion. Doses of 40 mg. of ammonium carbonate intravenously, equivalent to 1 gm. in man, at times failed to produce any increased secretion. In one instance 50 mg. of ammonium chloride intravenously, euqivalent to 1.25 gm. in man, failed to increase secretion. The dosage with which they obtained results was far in excess of that usually employed by the clinician, and therefore it may be said that they have not shown that in man these drugs in the ordinary therapeutic dose acts as expectorants. When they obtained results the increased secretion appeared in about ten minutes and was transitory in character, rarely lasting more than twenty minutes.

On account of the conflicting reports upon the action of the ammonium salts on bronchial secretion the following experimental work was carried out. Oblong pieces of filter paper of uniform weight and size, 6 x 12 cm., were rolled in such a manner so as to fit into the trachea and still leave a lumen of about 1 cm. Dogs averaging about 7 kilos were anesthetized by giving 5 gm. of chloretone in alcohol. The trachea was then severed transversely, just below the larynx, all bleeding stopped by means of the cautery, and a weighed rolled filter paper introduced. This came in close contact with the mucosa for a distance of about 6 cm. Such a filter was left in place ten minutes, then reweighed, and the increase taken as an index of the amount of secretion from the mucosa. This should also include some of the moisture in the expired air and mucus carried up from below. After two control readings of ten minutes each the ammonium carbonate in moderate doses was injected directly into the duodenum, and then another series of readings was taken, each of ten minutes, and continued for thirty minutes or more. Four animals in all were used.

The following results were obtained with ammonium carbonate:

Dog I, 7.2 kilos, received 5 gm. chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.2 and 0.12 gm. The increase in weight after 0.3 gm. of ammonium carbonate for three periods of ten minutes each was 0.18, 0.14, 0.16 gm. respectively.

Dog II, 6.5 kilos, received 5 gm. chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control periods

0.9 and 0.4 gm. respectively. The increase in weight after 0.25 gm. of ammonium carbonate for three ten-minute periods was 0.4, 0.4, and 0.4 gm. respectively.

Dog III, 7 kilos, received 5 gm. chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control readings 0.19 and 0.17 gm. respectively. The increase in weight after 0.5 gm. of ammonium carbonate for three periods was 0.17, 0.16, and 0.17 gm. respectively.

Dog IV, 7.5 kilos, received 5 gm. of chloretone in 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.2 and 0.14 gm. respectively. The increase in weight after 0.25 gm. of ammonium carbonate for three ten-minute periods was 0.14, 0.12, and 0.12 gm. respectively.

These experiments show that at least by the method pursued ammonium carbonate in what would be called moderate laboratory doses for a dog does not increase bronchial secretion. The dosage varied from 0.25 to 0.5 gm., equivalent to 2 to 4 gm. for a 65 kilo man, an amount considerably in excess of the ordinary therapeutic dose.

Both experimental and clinical evidence would indicate that the iodides cause increased secretion of bronchial mucus. Henderson and Taylor, from their experimental report, believe that this must be due to reflex stimulation of the bronchial centre from the stomach, as in their experiments iodides used intravenously did not modify the bronchial secretion. The iodides, as shown by Baehr and Pick and others, also cause dilatation of the bronchioles. It is possible this may play some role in facilitating the removal of mucus.

Many of the drugs having an emetic action also act as expectorants. Attention has already been called to the apparent intimate relation between the salivary and bronchial gland centre. The most important members of this group are apomorphin and ipecac. Both of these in non-emetic doses are supposed to cause increased bronchial secretion. Apomorphin probably acts chiefly by direct stimulation of the bronchial gland centre; ipecac both centrally and reflexly from the stomach. These drugs when pushed to the point where they have an emetic action may possibly through their vagus action also cause increased peristalsis of the smaller bronchioles. Senega, according to Henderson and Taylor, probably acts as an expectorant by effecting the bronchial gland centre reflexly from the stomach. Pilocarpin stimulates the bronchial glands directly.

Rossbach, Calvert, and Henderson and Taylor agree that ipecac and apomorphin act as expectorants in animals. Calvert failed to obtain results with senega, but Henderson and Taylor produced marked increased bronchial secretion in cats. Henderson and Taylor also obtained positive results with antimony and tincture of squill. The uniformity of these results leaves no doubt that in the doses used these drugs act as expectorants on dogs and cats. Henderson and Taylor call attention to one point, namely, that the bronchial gland centre is easily depressed and then fails to act. Especially with apomorphin a slight excess in dosage by depressing this centre would lessen bronchial secretion. They raise the question whether in diseased conditions with marked circulatory disturbance the bronchial gland centre would react as in the normal.

The dosage employed in all this experimental work was quite large. Henderson and Taylor gave 1 c.c. of the fluidextract of ipecac intravenously and 2 c.c. of the wine of ipecac by the mouth to a 2¼ kilo cat. This would be equivalent to 25 and 50 c.c. in man. This dose is, of course, far in excess of that employed clinically. Their results with senega and quill were obtained by using 2 c.c. of the tincture of each in a 2.5 kilo cat: here, again, doses far in excess of that employed in man. They have not, therefore, proved that any of these drugs are active in the ordinary therapeutic doses, which after all, from a clinical standpoint, is most important. For this reason we thought it desirable to repeat these experiments, using moderate doses.

The expectorant action of ipecac and apomorphin was tested on four dogs. The method of procedure differed very slightly from that used in the experiments with ammonium carbonate. After severing the trachea the roll of filter paper was introduced into the upper portion rather than the lower, as in the previous experiments. This method offers two advantages: (1) that absorption of moisture from the expired air is avoided; and (2) only mucus from the surface in contact with the filter paper is obtained, as in the previous method much mucus may be carried upward by ciliary action.

Chloretone was employed as an anesthetic in three of the animals, urethane in one. The emetin was injected directly into the stomach, the apomorphin into the duodenum. In each instance the filter paper was allowed to remain in contact with the mucosa ten minutes. Two control readings were taken before administering the drug. Readings were taken for at least forty minutes after giving the drug, which should be sufficient time to permit of a physiological action occurring.

The following results were obtained with emetin hydrochloride:

Dog V, 7.8 kilos, received 5 gm. of urethane and 2 gm. of chloretone in 20 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during the two control periods 0.65 and 0.69 gm. respectively. The increase in weight after 4 mg. of emetin hydrochloride for three periods of ten minutes each was 0.262, 0.0525, and 0.0495 gm. respectively.

Dog VI, 6.7 kilos, received 5 gm. of chloretone in 20 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.0613 and 0.062 gm. respectively. The increase in weight after 4 mg. of emetin hydrochloride, for three periods of ten minutes each, was 0.058, 0.056, and 0.05 gm. respectively.

The following results were obtained with apomorphin sulphate:

Dog VII, 9 kilos, received 2.5 gm. of chloretone in 15 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during two control periods was 0.08 and 0.0746 gm. respectively. The increase in weight after 2 mg. of apomorphin for three periods of ten minutes each was 0.0727, 0.0664, and 0.0643 gm.

Dog IX, 8 kilos, received 5 gm. of chloretone in 20 c.c. of 50 per cent. alcohol. Increase in weight of filter paper during the two control periods was 0.06 and 0.055 gm. respectively. The increase in weight after 2 mg. of apomorphin sulphate was 0.054, 0.058, and 0.055 gm. respectively.

It will be noticed that the first reading in each instance was considerable higher than the subsequent ones. This can probably be accounted for by mucus which had collected in the trachea, and, therefore, does not represent the real secretion during the period. At the beginning of the experiment there was frequently slight bleeding from the severed end of the trachea; this added to the weight of the filtered paper.

The apparently much greater secretion of mucus in Dogs I to V in both controls and after receiving the drug was due to the roll of filter paper being introduced in the lower segment of the severed trachea, so that much of the mucus on the filter paper was carried up by the cilia from below and also from moisture in the expired air. The filter paper was introduced into the upper end of the trachea in Dogs VI to IX, the increase in weight here probably being due almost entirely to mucus secreted from the surface covered by the filter paper.

I wish to express my appreciation of the valuable suggestions and assistance rendered by Prof. A. P. Matthews, of the University of Chicago.

SUMMARY. Ammonium carbonate and ammonium chloride and the emetic group of expectorants, as apomorphin and ipecac, when given in sufficiently large doses to animals, increase bronchial secretion. Ammonia salts per os, in moderate doses equivalent to 2 mg. in an adult man, do not increase bronchial secretion in the dog. Apomorphin and emetin when given to dogs in doses considerably greater than the ordinary therapeutic dose for man do not excite increased bronchial secretion.

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RELATIVE PULMONIC INSUFFICIENCY.

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In the study of the valvular diseases of the heart, a general agreement among clinicians may be noted in almost every field excepting the one we are to study.

Mackenzie, Dieulafoy, and many other writers do not even mention in their text-books the possibility of relative insufficiency at the pulmonary orifice. Jurgensen was evidently familiar with the murmur, but apparently failed to interpret it correctly. He states,[1] in describing the different types of murmur to be found in mitral stenosis, that "the diastolic murmur is also heard at times in the second left intercostal space, in the region of the pulmonary artery or a little outward from that point. At times the murmur is heard a little more distinctly in that locality than at the apex, especially when a systolic murmur is also present at the latter." It is certainly a most striking circumstance that he describes so closely the murmur we study in the very type of case in which it is most frequently noted. He makes no direct mention elsewhere of the lesion we are considering.

Among the authors at hand who mention the phenomenon definitely are Colbeck, who states that "relative incompetence of the pulmonic valve does sometimes occur, but the lesion is decidedly rare. It . . . may obtain in cases of mitral stenosis."

Satterthwaite states that "temporary insufficiency is doubtless of common occurrence."

Osler[2] says that "both Gibson and Graham Steell have called attention to the possibility of leakage through these valves in cases of great increase of pressure in the pulmonary artery, and to a soft diastolic murmur heard under these circumstances, which Steell calls "the murmur of high pressure in the pulmonary artery."

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[1] Nothnagel's Encyclopedia, Diseases of the Heart.

[2] Eighth edition.